1,185,080

PATENT SPECIFICATION

NO DRAWINGS

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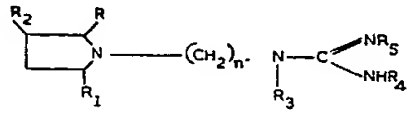
COMPLETE SPECIFICATION

Pyrrolidines

We BEECHAM GROUP LIMITED, a British Company, of Beecham House, Great West Road, Brentford, Middlesex do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to novel pyrrolidinoguanidine compounds that possess good blood pressure lowering activity with low side effects.

Accordingly the present invention provides pyrrolidinoguanidine compounds of the formula (I):



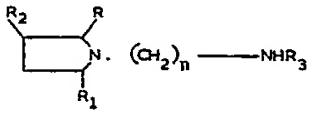
(I)

and non-toxic acid-addition salts thereof, wherein R, R_1 and R_3 are each a hydrogen atom or lower alkyl group; R_2 is a lower alkyl or cycloalkyl group; R_4 and R_5 are each a hydrogen atom or lower alkyl group and one of R_4 and R_5 may also be an amino or nitro group, or R_4 and R_5 form an ethylenic bridge $—CH_2CH_2—$; and n is 2 to 8.

The compounds of this invention may exist as cis and transisomers, and it is intended that these forms should be included. Since the compounds also contain asymmetric carbon atoms, they may exist in optically active forms, and again it is intended that these forms shall be included in the invention.

As used herein, the term "lower alkyl" is intended to refer to alkyl groups containing 1 to 6 carbon atoms.

The invention also provides a process for preparing the compounds of formula (I), which process comprises reacting a pyrrolidinoalkylamine of formula (II):



(II)

wherein R, R_1, R_2, R_3 and n are as defined above, or a salt thereof, with a guanylating agent, preferably a S-alkylisothiourea or acid-addition salt thereof.

Suitable guanylating agents include:

(1) a O- or S-alkylisothiourea or an acid-addition salt thereof,
(2) cyanamide or a substituted cyanamide or alkali metal salts thereof,
(3) a salt of 1-guanylpyrazole or an alkylated 1-guanylpyrazole such as 1-guanyl-3, 5-dimethylpyrazole or 1-guanyl-3, 4-dimethylpyrazole,
(4) a S-alkylisothiosemicarbazide, when one of R_4 and R_5 is a NH_2 group,
(5) a N - alkyl - N' - nitro - N - nitroso - guanidine, when one of R_4 and R_5 is a NO_2 group,
(6) a 2-nitroaminoiminazoline when R_4 and R_5 form an ethylenic bridge.

Preferably the guanylating agent is a S-alkylisothiourea or acid-addition salt thereof, and this is heated with the amine or salt thereof in an inert solvent to give the compound of formula (I).

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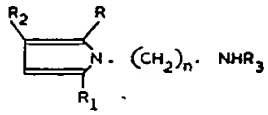
The starting pyrrolidinoalkylamines may be prepared by catalytically hydrogenating in solution a corresponding pyrrole of formula (III):



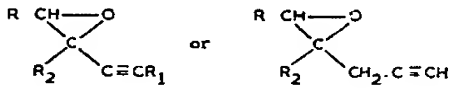
(III)

for example by using a rhodium/alumina or 5 to 10 % Pd/C catalyst. When R or R_1 is other than a hydrogen atom, mixtures of cis-trans isomers may be produced in this reaction.

Several methods may be used to prepare the pyrrolealkylamines of formula (III), and especially:

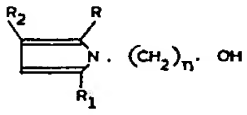
(1) reaction of an acetylenic chlorocarbinol ClCHR . CR_2(OH) . C: CR_1 or ClCHR . CR_2(OH) . CH_2 . C: CH with an amine NH_2 . $(CH_2)_n$. NH_2.

(2) reaction of an acetylenic epoxide of the formula:

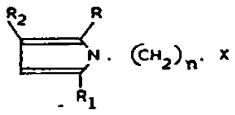


with an amine NH_2 . $(CH_2)_n$. NH_2.

(3) by converting a pyrrolealkanol of the formula:



into a reactive derivative of the formula:



wherein X is a halogen atom or the residue of a sulphonic acid, especially toluene-p-sulphonic acid, and reacting this compound with an amine R_3NH_2.

The pyrrolidinoalkylamines of formula (II) are also novel compounds, as are a number of the other intermediates described herein.

The invention also provides a pharmaceutical composition comprising a pyrrolidinoguanidine of formula (I), together with a pharmaceutically acceptable carrier. Suitable carriers include excipients, fillers, binders and sterile water to give compositions for administration by oral, parenteral and other routes.

The following Examples illustrate the invention:

Example 1

3 - Chloromethylbut - 1 - yn - 3 - ol (11.85 g.), ethylenediamine hydrate (60.8 g., 63.4 ml.) and ethanol, (40 ml.) were heated under reflux for 17 hours. Solvent and excess ethylenediamine were removed *in vacuo*, and 40% aqueous sodium hydroxide (10 ml.) was added. After removal of water from the mixture by azeotroping with benzene, removal of solvent gave an oil (9.67 g.), which was distilled to give 1 - (β - aminoethyl) - 3 - methylpyrrole (5.82 g., 47%), b.p. 65.5—66°C/2 mm., $n_D^{22.5}$ 1.5115 (Found: C, 67.75; H, 9.7; N, 22.6; $C_7H_{12}N_2$ requires: C, 68.0; H, 10.2; N, 22.9%).

This pyrrole (12.4 g.) was hydrogenated at room temperature and 500 p.s.i. pressure in ethanol (250 ml.) and 5N. hydrochloric acid (40 ml.), in the presence of 5% rhodium/alumina (5.0 g.) as catalyst. After 60 hours, the catalyst was filtered off and the solvent removed *in vacuo*. The residue was dissolved in water, basified with dilute sodium hydroxide solution, and the solution continuously extracted with ether, to give an oil (11.6 g.), Distillation afforded 1-(β-aminoethyl-3-methylpyrrolidine (8.72 g., 68%), b.p. 66°C/14 mm., n_D^{16} 1.4631 (Found: C, 65.8; H, 12.6; N, 22.1; $C_7H_{16}N_2$ requires: C, 65.5; H, 12.5; N, 21.9%).

The pyrrolidine (3.84 g.), S-methylisothiouronium sulphate (4.17 g.), ethanol (30 ml.) and water (20 ml.) were heated under reflux for 31/2 hours. After cooling, the solution was filtered, neutralised with 5N.sulphuric acid (6.0 ml.) and evaporated *in vacuo* to give a very viscous liquid, which, on boiling with ethanol, gave a colourless solid (7.31 g., 91%), m.p. 233—237°C (decomp.) Crystallisation from ethanol/water gave 1-(β-guanidinoethyl) - 3 - methylpyrrolidine sulphate (5.4 g., 68%), m.p. 243.5—245.5°C (decomp.) as colourless plates (Found: C, 35.4; H, 7.9; N, 21.2; S, 12.2; C $C_7H_{20}N_4SO_4$ requires: C, 35.8; H, 7.5; N, 20.9; S, 11.9%).

Example 2

3 - Chloromethylhept - 1 - yn - 3 - ol (48.15 g.), ethylenediamine hydrate (182.4 g., 190.2 ml.) and ethanol (120 ml.) were heated under reflux for 20 hours. Work-up as described in Example 1 gave 1-(β-aminoethyl)-3-n-butylpyrrole (24.1 g., 49%), m.p. 106—107°C/3 mm., n_D^{21} 1.4982 (Found: C, 72.2; H, 11.1; N, 17.1; $C_{10}H_{18}N_2$ requires: C, 72.3; H, 10.8; N, 16.9%).

Hydrogenation of this pyrrole (12.4 g.) for 48 hours at room temperature and 700 p.s.i. pressure, in ethanol (250 ml.) and 5N.hydrochloric acid (30 ml.) in the presence of 5% rhodium/alumina (4.0 g.) as catalyst, gave 1 - (β - aminoethyl) - 3 - n - butylpyrrolidine (7.91 g., 62%), b.p. 90—92°C/1 mm., n_D^{20} 1.4650.

The pyrrolidine (7.66 g.), S-methyl*iso*thiouronium sulphate (6.28 g.), ethanol (50 ml.) and water (30 ml.) were heated under reflux for 3 1/2 hours. Work-up as before gave 1 - (β - guanidinoethyl) - 3 - n - butyl - pyrrolidine sulphate (10.4 g., (73%), m.p. 194—197°C (decomp.), as colourless plates (Found: C, 42.2; H, 8.5; N, 18.15; S, 10.6; $C_{11}H_{26}N_4SO_4$ requires: C, 42.5; H, 8.4; N, 18.0; S, 10.3%).

Example 3

4 - Chloromethylpent - 1 - yn - 4 - ol (57 g.), anhydrous ethylenediamine (150 g.) 166 ml.) and ethanol (150 ml.) were heated under reflux for 17 hours. Work-up as described in Example 1 gave 1-(β-aminoethyl)-2,4-dimethylpyrrole (26.9 g., 45%), b.p. 72° C/0.9 mm, $n_D^{17.5}$ 1.5140 (Found: C, 69.6; H, 10.15; N, 20.2; $C_8H_{14}N_2$ requires: C, 69.6; H, 10.15; N, 20.3%).

Hydrogenation of the pyrrole (13.96 g.) under the same conditions as described in Example 1 gave 1-(β-aminoethyl)-2,4-dimethylpyrrolidine (6.98 g., 48%), b.p. 71° C/14 mm., n_D^{17} 1.4578 (Found: C, 67.2; H, 13.2; N, 19.7; $C_8H_{18}N_2$ requires: C, 67.6; H, 12.7; N, 19.7%).

Alternatively, the hydrogenation may be carried out using glacial acetic acid or aqueous acetic acid as solvent instead of ethanol-5N.hydrochloric acid. Also, the catalyst may be changed from 5% rhodium/alumina to 5% palladium/charcoal or 10% palladium/charcoal. The yields of the hydrogenation vary from 40 to 60%.

Treatment of the pyrrolidine (6.59 g.) with S-methyl*iso*thiouronium sulphate (6.45 g.) in aqueous ethanol under reflux for 3 1/2 hours, followed by work-up as described in Example 1, gave 1-(β-guanidinoethyl)-2,4-dimethylpyrrolidine sulphate hydrate (6.46 g. 50%), m.p. 291; 292°C (decomp) ex-acetone/water (Found: C, 36.1; H, 8.3; N, 18.9; S, 10.8; $C_9H_{22}N_4SO_4.H_2O$ requires: C, 36.0; H, 8.0; N, 18.7; S, 10.7%).

Example 4

3 - Chloromethylhex - 1 - yn - 3 - ol (15.8 g.) anhydrous ethylenediamine (39 g., 43.5 ml.) and ethanol (50 ml.) were heated under reflux for 21 hours. Work-up as described in Example 1 gave 1-(β-aminoethyl)-3-n-propylpyrrole (10.8 g., 66%), b.p. 58—60°C/0.1 mm. $n_D^{18.5}$ 1.4990 (Found: C, 71.0; H, 10.7; N, 18.3; $C_9H_{16}N_2$ requires: C, 71.1; H, 10.5; N, 18.4%).

Hydrogenation of the pyrrole (9.4 g.) under the same conditions as described in Example 1 gave 1-(β-aminoethyl)-3-n-propylpyrrolidine (7.2 g., 74%), b.p. 59.5—60°C/0.7 mm., $n_D^{17.5}$ 1.4641 (Found: C, 69.3; H, 13.0; N, 16.9; $C_9H_{20}N_2$ requires : C, 69.25; H, 12.8; N, 17.9%).

Treatment of the pyrrolidine (4.0 g.) with S-methyl*iso*thiouronium sulphate (3.6 g.) in aqueous ethanol under reflux for 3 1/2 hours, followed by work-up as described in Example 1, gave 1 - (β - guanidinoethyl) - 3 - n - propylpyrrolidine sulphate hemihydrate (2.4 g., 32%), m.p. 300°C ex-ethanol/water (Found: C, 39.2; H, 8.0; N, 18.2; S, 11.1; $C_{10}H_{24}N_4SO_4.\ 1/2H_2O$ requires; C, 39.4; H, 8.2; N, 18.3; S, 10.5%).

Example 5

4 - Chloro - 3 - phenylbut - 1 - yn - 3 - ol (60.2 g.), anhydrous ethylene diamine (108.0 g., 120 ml.) and ethanol (200 ml.) were heated under reflux for 24 hours. Work-up as described in Example 1 gave 1-(β-aminoethyl)-3-phenylpyrrole (33.1 g., 54%), b.p. 116—122°C/0.06 mm., n_D^{19} 1.6195, characterised as the hydrochloride m.p. 204—207° C (decomp.) (Found: C, 64.7; H, 7.0; N, 12.5; Cl, 16.3; $C_{12}H_{14}N_2.HCl$ requires: C, 64.7; H, 6.7; N, 12.6; Cl, 16.0%).

Hydrogenation of the pyrrole (10 g.) under the same conditions as described in Example 1 gave 1 - (β - aminoethyl - 3 - cyclohexyl - pyrrolidine (4.2 g., 41%), b.p. 90°—91°C/0.4 mm., n_D^{18} 1.4938 (Found: C, 73.75; H, 12.5; N, 13.85; $C_{12}H_{24}N_2$ requires: C, 73.5; H, 12.2; N, 14.3%).

Treatment of the pyrrolidine (9.8 g.) with S-methyl*iso*thiouronium sulphate (6.7 g.) in aqueous ethanol under reflux for 3 1/2 hours, followed by work-up as described in Example 1, gave 1 - (β - guanidinoethyl) - 3 - cyclo - hexylpyrrolidine sulphate sesquihydrate (14.4 g., 81%), m.p. 208—211°C (decomp.) ex-ethanol/water (Found: C, 43.1; H, 8.25; N, 15.2; S, 9.2; $C_{12}H_{28}N_4SO_4.3/2H_2O$ requires: C, 43.0; H, 8.55; N, 15 4; S, 8.8%).

Example 6

3 - Chloromethylpent - 1 - yn - 3 - ol (22.4 g.) anhydrous ethylenediamine (60.1 g., 67 ml.) and ethanol (100 ml.) were heated under reflux for 24 hours. Work-up as described in Example 1 gave 1-(β-aminoethyl)-3-ethylpyrrole (14.4 g., 62%), b.p. 64.5—65°C.9 mm., n_D^{20} 1.5067 (Found: C, 69.2; H, 10.3; N, 20.1: $C_8H_{14}N_2$ requires: C, 69.6; H, 10.1; N, 20.3%).

Hydrogenation of the pyrrole (12.3 g.) under the same conditions as described in Example 1 gave 1-(β-aminoethyl)-3-ethylpyrrolidine (7.3 g., 57%), b.p. 79—81°C/14 mm., $n_D^{18.5}$ 1.4633 (Found: C, 67.3; H, 12.7; N, 19.65; $C_8H_{18}N_2$ requires: C, 67.6; H, 12.7; N, 19.7%).

Treatment of the pyrrolidine (5.0 g.) with S-methyl*iso*thiouronium sulphate (4.9 g.) in aqueous ethanol under reflux for 3 1/2 hours, followed by work-up as described in Example 1, gave 1-(β-guanidinoethyl)-3-ethypyrrolidine sulphate (7.5 g., 74%), m.p. 259—261°C (decomp.) ex-ethanol/water (Found: C, 38.0; H, 7.9; N, 19.4; S, 11.3; $C_9H_{22}N_4SO_4$ requires: C, 38.3; H, 7.8; N, 19.85; S, 11.35%).

Example 7

4 - Chloromethylhex - 1 - yn - 4 - ol (52.2 g.), anhydrous ethylenediamine (122.0 g., 136 ml.) and ethanol (200 ml.) were heated under reflux for 30 hours. Work-up as described in Example 1 gave 1-(β-aminoethyl)-4-ethyl-2-methylpyrrole (36.7 g., 68%), b.p. 82—87°C/1.3—1.8 mm., n_D^{20} 1.5087 (Found: C, 71.0; H, 10.5; N, 18.3; $CC_{10}H_{16}N_2$ requires: C 71.1; H, 10.5; N, 18.4%).

Hydrogenation of the pyrrole (33.1 g.) under the same conditions as described in Example 1 gave 1-(β-aminoethyl)-4-ethyl-2-methylpyrrolidine (12.2 g., 36%), b.p. 88—89.5°C/15 mm., $n_D^{16.5}$ 1.4598, characterised as the di-toluene-p-sulphonate, m.p. 157—158°C (Found: C, 54.4; H, 7.2; N, 5.6; S, 13.2; $C_{23}H_{36}N_2S_2O_6$ requires: C, 55.2; H, 7.2; N, 5.6; S, 12.8%)

Treatment of the pyrrolidine (6.0 g.) with S-methyl*iso*thiouronium sulphate (5.4 g.) in aqueous ethanol under reflux for 3 hours, followed by work-up as described in Example 1, gave 1 - (β - guanidinoethyl) - 4 - ethyl - 2-methylpyrrolidine sulphate (8.0 g., 70%), m.p. 248—250.5°C (decomp.) ex-ethanol/water (Found: C, 40.7; H, 8.2; N, 18.8; S, 11.2; $C_{10}H_{24}N_4SO_4$ requires: C, 40.6; N, 8.1; N, 18.9; S, 10.8%).

Example 8

3-Bromopropyne (71.5 g., 45 ml.) was dissolved in ether (200 ml.) and a 10 ml. portion of the solution was added to magnesium turnings (14.65 g.) covered with ether (200 ml.). When the reaction commenced the mixture was cooled to −10°C and the remainder of the 3-bromopropyne solution was added dropwise at −10°C. 1-Chloro-3,3-dimethylbutan-2-one (55.7 g.) in benzene (200 ml.) was then added dropwise and the mixture was stirred for a further 4 hours at −10°C. 5N sulphuric acid (250 ml.) was then added, followed by water (250 ml.). After filtration, the product was extracted into ether and the ether portion was washed with water, saturated sodium hydrogen carbonate solution, and finally water. After drying over magnesium sulphate, the ether was removed under reduced pressure. Careful fractionation of the crude oil (65.3 g.) effected separation into 4-chloromethyl-5,5-dimethylhex-1-yn-4-ol (4.2 g., 6%), b.p. 65—68° C/3.6 mm., $n_D^{14.5}$ 1.4828, and 4-t-butyl-4,5-epoxypent-1-yne (7.9 g., 14%), b.p. 36—38.5°C/3.5 mm., n_D^{17} 1.4482.

4 - Chloromethyl - 5, 5 - dimethylhex - 1-yn-4-ol (3.0 g.), anhydrous ethylenediamine (6.2 g., 6.7 ml.) and ethanol (100 ml.) were heated under reflux for 24 hours. Work-up as described in Example 1 gave 1-(β-aminoethyl) - 4 - t - butyl - 2 - methylpyrrole (2.2 b., 71%), b.p. 60—62°C/0.05 mm., n_D^{17} 1.5007 (Found: C, 73.1; H, 11.3; N, 15:1; $C_{11}T_{2n}N_2$ requires: C, 73.3; H, 11.1; N, 15.6%).

Alternatively, 4 - t - butyl - 4,5 - epoxy - pent-1-yne (6.85 g.), anhydrous ethylenediamine (17.75 g., 19.4 ml.) and ethanol (100 ml.) were heated under reflux for 24 hours. Solvent and excess ethylendiamine were removed *in vacuo* and water was removed by azeotroping with benzene. Removal of solvent and distillation gave 1-(β-aminoethyl)-4-t-butyl-2-methylpyrrole (6.4 g., 72%).

Hydrogenation of the pyrrole (7.0 g.) under the same conditions as described in Example 1 gave 1 - (β - aminoethyl) - 4 - t - butyl - 2-methylpyrrolidine (4.3 g., 60%), b.p. 105—109°C/14 mm., n_D^{21} 1.4618 (Found: N, 14.8; $C_{11}H_{24}N_2$ requires: N, 15.2%).

Treatment of the pyrrolidine (3.3 g.) with S-methyl*iso*thiouronium sulphate (2.5 g.) in aqueous ethanol under reflux for 3 1/2 hours, followed by work-up as described in Example 1, gave 1 - (β - guanidinoethyl) - 4 - t - butyl-2-methylpyrrolidine sulphate hemihydrate (4.2 g., 70%), m.p. 246—249°C (decomp.) ex-ethanol/water (Found: C, 43.4; H, 8.7; N, 16.5; S, 9.8 $C_{12}H_{28}N_4SO_4$. 1/2 H_2O requires C, 43.2; H, 8.7; N, 16.8; S, 9.6%).

Example 9

4 - Chloro - 3 - methylpent - 1 - yn - 3 - ol (143.3 g.) and anhydrous ethylenediamine (450 g., 500 ml.) were heated under reflux for 6 days. Work-up as described in Example 1 gave 1 - (β - aminoethyl) - 2,3 - dimethyl - pyrrole (60.0 g., 43%), b.p. 72°C/0.9 mm., n_D^{19} 1.5162 (Found: C. 69.75; H, 10.3; N, 20.5; $C_8H_{14}N_2$ requires: C, 69.6; H, 10.15; N, 20.3%).

Hydrogenation of the pyrrole (27.6 g.) under the same conditions as described in Example 1 gave 1 - (β - aminoethyl) - 2.3 - dimethylpyrrolidine (16.0 g., 56.5%), b.p. 81—83°C/18 mm., n_D^{20} 1.4640, characterised as the dipicrate, m.p. 320—321°C (Found: C, 40.0; H, 4.1; N, 18.5; $C_{20}H_{24}N_8O_{14}$ requires: C, 40.0; H, 4.0; N, 18.7%).

Treatment of the pyrrolidine (8.0 g.) with S-methyl*iso*thiouronium sulphate (7.8 g.) in aqueous ethanol under reflux for 5 hours, followed by work-up as described in Example 1, gave 1 - (β - guanidinoethyl) - 2,3 - dimethylpyrrolidine sulphate hemihydrate (13.6 g. 86%), m.p. 272—274°C (decomp.) (Found: C, 37.35; H, 7.8; N, 19.6; S, 11.2;

$C_9H_{22}N_4SO_4$. 1/2 H_2O requires: C, 37.15; H, 7.9; N, 19.2; S, 11.0%).

1 - (β - Aminoethyl) - 2, 3 - dimethyl - pyrrolidine prepared as described above is obtained as a mixture of *cis* and *trans* isomers in the ratio 65 : 35 respectively. These isomers may be separated by preparative scale gas-liquid chromatography using a column of 20% silicone oil DC 550 on Celite (Registered Trade Mark) nitrogen as carrier gas.

Treatment of each of the pure isomers separately with S-methyl*iso*thiouronium sulphate in the usual way, followed by work-up as described in Example 1, gave cis-2,3-dimethyl - 1 - (β - guanidinoethyl)pyrrolidine sulphate, m.p. 292—295°C (decomp.) (Found: C, 38.6; H, 8.0; N, 20.0; S, 11.4; $C_9H_{22}N_4SO_4$ requires: C, 38.3; H, 7.8; N, 19.9; S, 11.35%) and trans-2,3-dimethyl-1-(β-guanidinoethyl)pyrrolidine sulphate hemihydrate, m.p. 294—295° (decomp.) (Found: C, 37.4; H, 7.8; N, 18.7; S, 11.0; $C_9H_{22}N_4SO_4$. 1/2 H_2O requires: C, 37.15; H, 7.9; N, 19.2; S, 11.0%).

Example 10

3-Chlorobutan-2-one (210 g.) in benzene (500 ml) was; added dropwise to a stirred solution of propargylmagnesium bromide (prepared from 3-bromopropyne (357 g., 225 ml.) and magnesium turnings (72 g.) as described in Example 8) in ether at —10°C. Work-up as described in Example 8 gave 5-chloro - 4 - methylhex - 1 - yn - 4 - ol (230.9 g., 80%), b.p. 35—40°C/0.7—1.0 mm., n_D^{19} 1.4702 (Found: Cl, 23.5; $C_7H_{11}C1O$ requires: Cl, 24.2%).

5 - Chloro - 4 - methylhex - 1 - yn - 4 - ol (146.5 g.) and ethylenediamine (360 g., 400 ml.) were heated under reflux for 3 days. Work-up as described in Example 1 gave 1 - (β - aminoethyl) - 2,3,5 - trimethyl - pyrrole (115.1 g., 7%), b.p. 60—65°C/0.01 mm., $n_D^{21.5}$ 1.5171 (Found: C, 70.3; H, 10.6; N, 18.1; $C_9H_{16}N_2$ requires: C, 71.1; H, 10.5; N, 18.4%).

Hydrogenation of the pyrrole (20 g.) under the same conditions as described in Example 1 gave 1 - (β - aminoethyl - 2,3,5 - trimethyl - pyrrolidine (15.6 g., 77% b.p. 78.5—80°C/11 mm., n_D^{20} 1.4995, characterised as the dipicrate, m.p. 227—228°C (Found: C, 41.0; H, 4.3; N, 18.4; $C_{21}H_{26}N_8O_{14}$ requires: C, 41.05; H, 4.2; N, 18.25%).

Treatment of the pyrrolidine (7.1 g.) with S-methyl*iso*thioronium sulphate (6.3 g.) in aqueous ethanol under reflux for 4 hours, followed by work-up as described in Example 1, gave 1 - (β - guanidinoethyl) - 2,3,5 - trimethylpyrrolidine sulphate (9.7 g., 72%), m.p. 275—278°C (decomp.) ex-ethanol/water (Found: C, 40.3; H, 8.2; N, 18.7; S, 10.9; $C_{10}H_{24}N_4SO_4$ requires: C, 40.6; H, 8.1; N, 18.9; S, 10.8%).

Example 11

Ethylmagnesium bromide (prepared from ethyl bromide (164.0 g., 113 ml.) and magnesium turning (36.0 g.) in ether) was added during 1 hour to ether (700 ml.) saturated with 1-butyne. During the addition the internal temperature was maintained below 10°C and a steady stream of 1-butyne was bubbled into the reaction mixture. The mixture was then cooled to 5°C and chloroacetone (93 g.) was added dropwise. After stirring overnight at room temperature, saturated ammonium chloride solution (250 ml.) was added cautiously and the resulting inorganic precipitate was filtered off and washed with ether. The filtrate was washed with water, dried over magnesium sulphate, and evaporated *in vacuo* to give an oil (136 g.). Careful fractionation yielded 5-chloromethylhex-3-yn-5-ol (57.5 g., 39%), b.p 81°C/11 mm., n_D^{21} 1.4710 (Found: C, 57.2; H, 7.6; Cl, 24.5; $C_7H_{11}C1O$ requires: C 57.3; H, 7.5; Cl, 24.2%). 2 - Chloromethyl - butan - 2 - ol (24.0 g., 20%) was also isolated due to reaction between unchanged ethylmagnesium bromide and chloroacetone.

5 - Chloromethylhex - 3 - yn - 5 - ol (48.8 g.), anhydrous ethylenediamine (108.0 g., 120.0 ml.) and ethanol (150 ml.) were heated under reflux for 24 hours. Work-up as described in Example 1 gave 1-(β-aminoethyl-2-ethyl-4-methylpyrrole (36.8 g., 73%), b.p. 79—80°C/0.12 mm., n_D^{21} 1.5085 (Found: C, 70.4; H, 10.8; N, 18.0; $C_9H_{16}N_2$ requires: C, 71.1; H, 10.5; N, 18.4%).

Hydrogenation of the pyrrole (20 g.) under the same conditions as described in Example 1 gave 1 - (β - aminoethyl) - 2 - ethyl - 4 - methylpyrrolidine (18.1 g., 88%), b.p. 82°C/12 mm., n_D^{21} 1.4610, characterised as the dipicrate, m.p. 180—181°C (Found: C, 41.3; H, 4.3; N, 18.1; $C_{21}H_{26}N_8O_{14}$ requires: C, 41.05; H, 4.2; N, 18.25%).

Treatment of the pyrrolidine (7.6 g.) with S-methyl*iso*thiouronium sulphate (6.95 g). in aqueous ethanol under reflux for 4 1/2 hours, followed by work-up as described in Example 1, gave 1-(β-guanidinoethyl)-2-ethyl-4-methylpyrrolidine sulphate (10.6 g., 71%), m.p. 272—274° (decomp.) ex-ethanol/water (Found: C, 40.05; H, 8.2; N, 18.6; S, 11.4; $C_{10}H_{24}N_4SO_4$ requires: C, 40.6; H, 8.1; N, 18.9; S, 10.8%).

Example 12

4 - Chloromethylpent -) 1 - yn - 4 - ol (25 g.) 1.3-diaminopropane (84.5 g., 95 ml.) and ethanol (200 ml.) were heated under reflux for 23 hours. Solvent was removed *in vacuo*, 40% aqueous sodium hydroxide solution (18.9 ml.) was added, and the mixture was extracted with chloroform. The chloroform extracts were concentrated to small bulk *in vacuo* and the concentrated solution was then extracted with petroleum-

ether (60—80°C.) After drying over magnesium sulphate, the petroleum-ether was evaporated *in vacuo* to give a crude oil (17.1 g.). Distillation afforded 1-(γ-aminopropyl)-2,4 - dimethylpyrrole (14.1 g., 50%), b.p. 78—80°C/1 mm., n_D^{20} 1.5081 (Found: C, 71.55; H, 10.6; N, 18.4; $C_9H_{16}N_2$ requires: C, 71.1; H, 10.5; N, 18.4%).

Hydrogenation of the pyrrole (11.6 g.) under the same conditions as described in Example 1 gave 1-(γ-aminopropyl)-2,4-dimethylpyrrolidine (8.0 g., 66%), b.p. 82—86°C/13 mm., n_D^{21} 1.4595, characterised as the dipicrate, m.p. 195—198°C (Found: C, 41.0; H, 4:4; N, 18.2; $C_{21}H_{26}N_8O_{14}$ requires: C, 41.05; H, 4.2; N, 18.25%).

Treatment of the pyrrolidine (1.32 g.) with S-methylisothiouronium sulphate (1.18 g.) in aqueous ethanol under reflux for 3 1/2 hours, followed by work-up as described in Example 1, gave 1-(γ-guanidinopropyl)2,4-dimethylpyrrolidine sulphate hemihydrate (1.4 g., 56%), m.p. 292—294°C (decomp.) ex-ethanol/water (Found: C, 39.8; H, 8.2; N, 18.3; S, 10.6; $C_{10}H_{24}N_4SO_4$. 1/2 H_2O requires: C, 39.4; H, 8.2; N, 18.3; S, 10.5%).

Example 13

4 - Chloromethylpent - 1 - yn - 4 - ol (17 g.), 8-diamino-n-octane (60 g.) and ethanol (150 ml.) were heated under reflux for 24 hours. Work-up as described in Example 12 gave 1-(ω-amino-n-octyl)-2,4-dimethylpyrrole (17.2 g., 60%), b.p. 112—114°C/0.02 mm., n_D^{20} 1.4919 (Found: C, 75.7; H, 12.0; N, 12.4; $C_{14}H_{26}N_2$ requires: C, 75.8; H, 11.7; N, 12.6%).

Hydrogenation of the pyrrole (14.7 g.) under the same conditions as described in Example 1 gave 1-(ω-amino-n-octyl)-2,4-dimethylpyrrolidine (10.0 g., 50%), b.p. 96° C/0.35 mm., n_D^{23} 1.4620 (Found: C, 73.8; H, 13.5; N, 12.2; $C_{14}H_{30}N_2$ requires: C, 74.3; H, 13.3; N, 12.4%).

Treatment of the pyrrolidine (4.0 g.) with S-methyl*iso*thioronium sulphate (2.5 g.) in aqueous ethanol under reflux for 3 1/2 hours, followed by work-up as described in Example 1, gave 1-(ω-guanidino-n-octyl)-2,4-dimethylpyrrolidine sulphate hydrate (6.5 g., 95%) as a hygroscopic gum (Found: C, 47.1; H, 9.75; N, 14.5; S, 8.7; $C_{15}H_{32}N_4SO_4.H_2O$ requires: C, 46.9; H, 9.4; N, 14.6; S, 8.3%).

Example 14

To a stirred solution of 1-(β-aminoethyl)-2,4-dimethylpyrrolidine (14.2 g.; prepared as described in Example 3) in 50% aqueous ethanol (100 ml.), N-methyl-N^1-nitro-N-nitroso-guanidine (10.1 g.) was added in small portions keeping the temperature of the mixture below 20°C. After stirring overnight, the crystalline product was filtered off, washed with 50% aqueous ethanol, and dried dover phosphorus pentoxide. Recrystallisation from ethyl acetate gave N-β-(2,4-dimethyl - 1 - pyrrolidinyl) ether - N^1 - nitroguanidine (7.45 g., 46%), m.p. 121°C as colourless plates (Found: C, 47.3; H, 8.4; N, 30.9; $C_9H_{19}N_5O_2$ requires: C, 47.2; H, 8.3; N, 30.6%).

The guanidine (6.9 g.) was dissolved in butanone and a current of anhydrous hydrogen chloride was passed through the solution causing the precipition of the monohydrochloride (7.95 g. 99%) m.p. 158°C. Recrystallisation from ethanol gave colourless plates, m.p. 158°C (Found: C, 40.6; H, 7.55; N, 26.45; Cl, 13.5; $C_9H_{20}N_5ClO_2$ requires: C, 40.7; H, 7.5; N, 26.4; Cl, 13.4%).

Example 15

1 - (β - Aminoethyl) - 2,4 - dimethyl - pyrrolidine (7.1 g.; prepared as described in Example 3) was treated with S-methyl*iso*-thiosemicarbazide hydriodide (8.2 g.) in ethanol at room temperature for 30 hours. The mixture was then evaporated *in vacuo* and the oil residue was dissolved in the minimum of ethanol. Addition of ether caused the precipitation of a colourless solid (9.1 g., 79%), m.p. 110—111°C, which, on crystallisation from ethanol/ether, gave N-amino - N^1 - β - (2,4 - dimethyl - 1 - pyrrolidinyl)ethylguanidine hydroidide (7.75 g., 67%), m.p. 113—114°C as colourless plates (Found: C, 32.8; H, 6.6; N, 21.4; I, 38.4; $C_9H_{22}N_5I$ requires: C, 33.0; H, 6.7; N, 21.4; I, 38.8%).

Example 16

1 - (β - Aminoethyl) - 2,4 - dimethyl - pyrrolidine (21.9 g., prepared as described in Example 3) and 2-nitraminoimidazoline (4.4 g.) were mixed together in a Vigreux flask and heated in an oil-bath to 130°C. The initial vigorous reaction was allowed to moderate and the contents of the flask were then heated slowly up to 200°C and were maintained at this temperature for 10 minutes. The mixture was allowed to cool and excess β-pyrrolidinylethylamine was removed in vacuo (water-pump). Distillation then gave 1-(β-2'-imidazolinylaminoethyl)-2,4-dimethylpyrrolidine (6.35 g., 88%), b.p. 147—149°C/0.01 mm. as a colourless liquid which solidified on standing to give colourless hygroscopic crystals, m.p. 72—73°C.

The imidazoline (6.3 g.) was dissolved in ethanol and 5N, sulphuric acid (12.1 ml.) was added. Evaporation of the neutral solution to dryness under reduced pressure and crystallisation of the solid residue from ethanol/ethyl acetate gave the sulphate hydrate (8.7, 88%), m.p. 219—221°C as colourless plates (Found: C, 40.5; H, 8.15; N, 17.2; S, 10.3; $C_{11}H_{21}N_4SO_4.H_2O$ requires: C, 40.5; H, 8.0; N, 17.35; S, 10.4%).

EXAMPLE 17

4 - Chloromethylpent - 1 - yn - 4 - ol (132.5 g.), ethanolamine (366 g., 360 ml.), and ethanol (200 ml.) were refluxed for 24 hours. Work-up as described in Example 1 gave 2,4 - dimethyl - 1 - (β - hydroxyethyl) pyrrole (68.6 g., 50%), b.p. 76—78°C/0.4 mm., n_D^{20} 1.5094 (Found: C, 69.4; H, 9.6; N, 10.2; $C_8H_{13}NO$ requires: C, 69.1; H, 9.35; N, 10.1%).

Toluene-p-sulphonyl chloride (30 g.) was added to a solution of the β-pyrrolylethanol (20 g.) in pyridine (100 ml.) at 0°C. After 4 days at 0°C, the mixture was poured into ice-water (400 g.) with vigorous stirring. The resulting precipitate was filtered off, washed with ice-water, and dried *in vacuo* at room temperature. Crystallisation from a large volume of petroleum-ether (40—60°C) gave the tosylate (32.7 g., 76%), m.p. 93—94° C (decomp) as grey plates (Found: C, 60.8; H, 6.6; N, 4.5; S, 10.8; $C_{15}H_{19}NSO_3$ requires: C, 61.4; H, 6.5; N, 4.8; S, 10.9%).

The tosylate (28.2 g.) was added to 33% ethanolic methylamine solution (210 ml.) and the mixture was allowed to stand for 7 days at room temperature. Solvent and excess methylamine were removed *in vacuo*, 40% aqueous sodium hydroxide, (10 ml.) was added, and the solution was extracted thoroughly with ether. After drying over magnesium sulphate, evaporation of ether and distillation afforded 2,4 - dimethyl - 1 - (β - methylaminoethyl)pyrrole (6.7 g., 46%), b.p. 67—69°C/1.0 mm. n_D^{20} 1.4995, characterised as the picrate, m.p. 158°C (Found: C, 47.4; H, 5.1; N, 18.3; $C_{15}H_{19}N_5O_7$ requires: C, 47.25; H, 5.0; N, 18.35%).

Hydrogenation of this pyrole (5.9 g.) under the same; conditions as described in Example 1 gave 2,4 - dimethyl - 1 - (β - methyl - amino)ethylpyrrolidine (4.0 g., 66%), b.p. 89—90°C/25 mm., n_D^{21} 1.4490, characterised as the dipicrate, m.p. 141—142°C (decomp.) (Found: C, 41.0; H, 4:4; N, 18.2; $C_{21}H_{26}N_8O_{14}$ requires: C, 41.05; H, 4.2; N, 18.25%).

Treatment of the pyrrolidine (3.2 g.) with S-methyl*iso*thiuronium sulphate (2.9 g.) in aqueous ethanol under reflux for 16 hours, followed by work-up as described in Example 1, gave N - methyl - N - β - (2,4 - dimethyl - 1-pyrrolidinyl) ethylguanidine sulphate sesquihydrate (2.6 g., 40%), m.p. 254—258°C (decomp.) ex-ethanol/water (Found: C, 37.4; H, 7.5; N, 17.2; S, 9.4; $C_{10}H_{24}N_4SO_4.3/2\ H_2O$ requires: C, 37.2; H, 7.45; N, 17.35; S, 10.2%).

EXAMPLE 18

4 - Chloromethylpent - 1 - yn - 4 - ol (50 g.), 1,2-diaminopropane (165 g., 190 ml.) and ethanol (100 ml.) were heated under reflux for 19 hours. Work-up as described in Example 1 gave a colourless oil (26.9 g., 47%), b.p. 60—65°C/0.05 mm., n_D^{21} 1.5048, shown to be a 65:35 mixture of 1-(β-aminopropyl) - 2,4 - dimethylpyrrole and β - (2,4 - dimethyl - 1 - pyrrolyl) - propylamine respectively (Found: C, 69.75; H, 10.8; N, 18.0; $C_9H_{16}N_2$ requires: C, 71.1: H, 10.5; N, 18.4%).

This mixture (15.2 g.) of pyrroles was hydrogenated at room temperature and atmospheric pressure in ethanol (100 ml.) and 5N.hydrochloric acid (40 ml.), in the presene of 5% rodium/alumina (4.0 g.) as catalyst. After 24 hours, work-up as described in Example 1 gave a colourless oil (10.5 g., 67%), b.p. 78—82°C/14 mm., n_D^{19} 1.4526, shown to be a 63:37 mixture of 1-(β-aminopropyl) - 2,4 - dimethylpyrrolidine and β - (2,4 - dimethyl - 1 - pyrrolidinyl) propylamine respectively (Found: C, 69.0; H, 13.1; N, 17.9; $C_9H_{20}N_2$ requires: C, 69.25; H, 12.8; N, 17.95%).

Treatment of this mixture (5.0 g.) of pyrrolidines with S-methyl*iso*thiouronium sulphate (4.4 g.) in aqueous ethanol under reflux for 3 hours, followed by work-up as described in Example 1, gave a colourless crystalline mixture (9.5 g., 100%) of 1-(β-(guanidinopropyl) - 2,4 - dimethylpyrrolidine sulphate and β-(2,4-dimethyl-1-pyrrolidinyl)-propylguanidine sulphate. Recrystallisation from ethanol gave colourless plates (2.25 g.), m.p. 304—305°C (decomp.) (Found: C, 39.4; H, 8.15; N, 18.35; S, 10.65; $C_{10}H_{24}N_4SO_4.\ 1/2H_2O$ requires: C, 39.4; H, 8.2; N, 18.3; S, 10.5%).

EXAMPLE 19

A mixture of 1-guanyl-3,5-dimethylpyrazole nitrate and 1-(β-aminoethyl)-2,4-dimethylpyrrolidine (prepared as described in Example 3) was heated for 21/2 hours with stirring. The excess of amine was removed *in vacuo* and the residue was dissolved in water and converted to the desired 1-(β-guanidinoethyl) - 2,4 - dimethylpyrrolidine sulphate hydrate by treatment with a strong anion (sulphate) exchange resin. The resulting solution was evaporated under reduced pressure and the residue was recrystallised from aqueous ethanol; the product was identical with that obtained according to Example 3.

EXAMPLE 20

A solution of 1-(β-aminoethanol)-2,4-dimethylpyrrolidine (prepared as described in Example 3) in ethanol was neutralised with 5N.sulphuric acid, cyanamide was added and the mixture was heated under reflux for 6 hours. Removal of solvent *in vacuo* and crystallisation of the residue from aqueous ethanol gave 1-(β-guanidinoethyl-2,4-dimethylpyrrolidine sulphate hydrate, identical to the compound obtained according to Example 3.

EXAMPLE 21

A solution of 1-(β-aminoethyl)-2,4-di-

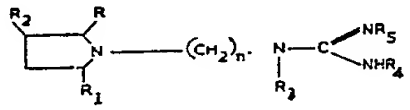
methylpyrrolidine (prepared as described in Example 3) in water was neutralised with 5N sulphuric acid, an equivalent amount of monosodium cyanamide was then added and the mixture was heated under reflux for 8 hours. The mixture was then treated with an equivalent amount of 5N sulphuric acid and evaporated *in vacuo*. Recrystallisation of the residue from ethanol/water gave the desired 1 - (β - guanidimethyl) - 2,4 - dimethyl - pyrrolidine sulphate hydrate; the product being identical to the compound obtained in Example 3.

EXAMPLE 22

1 - (β - aminoethyl) - 2,4 - dimethyl - pyrrolidine (prepared as described in Example 3) and o-methyl*iso*uronium sulphate were dissolved in aqueous ethanol and heated under reflux for 4 hours. After neutralisation with 5N sulphuric acid, the mixture was evaporated *in vacuo* and crystallisation of the residue from ethanol/water gave the desired 1 - (β - guanidinoethyl) - 2,4 - dimethyl - pyrrolidine sulphate hydrate; the product being identical to the compound obtained in Example 3.

WHAT WE CLAIM IS:—

1. Pyrrolidinoguanidine compounds of the formula (I):



(I)

and non-toxic acid-addition salts thereof, wherein R, R_1 and R_3 are each a hydrogen atom or lower alkyl group; R_2 is a lower alkyl or cycloalkyl group; R_4 and R_5 are each a hydrogen atom or lower alkyl group and one of R_4 and R_5 may also be an amino or nitro group, or R_4 and R_5 form an ethylenic bridge $—CH_2CH_2—$; and n is 2 to 8.

2. 1 - (β - Guanidinoethyl) - 3 - methyl - pyrrolidine and non-toxic acid addition salts thereof.

3. 1 - (β - Guanidinoethyl) - 3 - n - butyl - pyrrolidine and non-toxic acid addition salts thereof.

4. 1 - (β - Guanidinoethyl) - 2,4 - di - methylpyrrolidine and non-toxic acid addition salts thereof.

5. 1 - (β - Guanidinoethyl) - 3 - n - propyl-pyrrolidine and non-toxic acid addition salts thereof.

6. 1 - (β - Guanidinoethyl) - 3 - cyclo - hexylpyrrolidine and non-toxic acid addition salts thereof.

7. 1 - (β - Guanidinoethyl) - 3 - ethyl - pyrrolidine and non-toxic acid addition salts thereof.

8. 1 - (β - Guanidinoethyl) - 4 - ethyl - 2 - methylpyrrolidine and non-toxic acid addition salts thereof.

9. 1 - (β - Guanidinoethyl) - 4 - t - butyl - 2-methylpyrrolidine and non-toxic acid addition salts thereof.

10. 1 - (β - Guanidinoethyl) - 2,3 - di - methylpyrrolidine and non-toxic acid addition salts thereof.

11. 1 - (β - Guanidinoethyl) - 2,3,5 - tri - methylpyrrolidine and non-toxic acid addition salts thereof.

12. 1 - (β - Guanidinoethyl) - 2 - ethyl - 4-methylpyrrolidine and non-toxic acid addition salts thereof.

13. 1 - (γ - Guanidinopropyl) - 2,4 - di - methylpyrrolidine and non-toxic acid addition salts thereof.

14. 1 - (ω - Guanidino - n - octyl) - 2,4 - dimethylpyrrolidine and non-toxic acid addition salts thereof.

15. N - β - (2,4 - Dimethyl - 1 - pyrroli - dinyl)ethyl-N^1-nitroguanidine and non-toxic acid addition salts thereof.

16. N - Amino - N^1 - β - (2,4 - dimethyl - 1-pyrrolidinyl)ethylguanidine and non-toxic acid addition salts thereof.

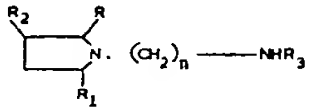
17. 1 - (β - 2^1 - Imidazolinylaminoethyl) - 2,4-dimethylpyrrolidine and non-toxic acid addition salts thereof.

18. N - Methyl - N - β - (2,4 - dimethyl - 1-pyrrolidinyl)ethylguanidine and non-toxic addition salts thereof.

19. 1 - (β - Guanidinopropyl) - 2,4 - di - methylpyrrolidine and non-toxic acid addition salts thereof.

20. β - (2,4 - Dimethyl - 1 - pyrrolidinyl) - propylguanidine and non-toxic acid addition salts thereof.

21. A process for preparing the compounds of formula (I) which process comprises reacting a pyrrolidinoalkylamine of formula (II):



(II)

wherein R, R_1, R_2, R_3 and n are as defined above, or a salt thereof with a guanylating agent.

22. A process as claimed in claim 21, wherein the guanylating agent is a O- or S-alkylisothiourea or an acid-addition salt thereof.

23. A process as claimed in claim 21, wherein the guanylating agent is cyanamide or a substituted cyanamide or alkali metal salts thereof.

24. A process as claimed in claim 21, wherein the guanylating agent is a salt of 1-guanylpyrazole or an alkylated 1-guanyl-pyrazole.

25. A process as claimed in claim 24, wherein the guanylating agent is 1-guanyl-3,5-dimethypyrazole.

26. A process for preparing pyrrolidinoguanidine compounds of formula (I) substantially as described with reference to any one of Examples 1 to 21 hereinbefore set forth.

27. Pyrrolidinoguanidine compounds of formula (I) when prepared by a process as claimed in any one of claims 21, 26 or 27.

28. A pharmaceutical composition comprising a pyrrolidinoguanidine compound of formula (I) or a non-toxic salt thereof, together with a pharmaceutically acceptable carrier.

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